

REMARKS

Claims 11–30 are pending.

Applicants' Statement on Substance of Examiner's Interviews

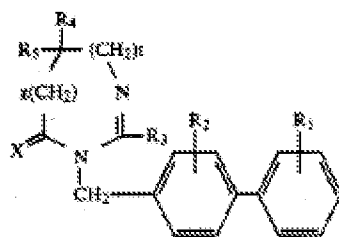
Applicants express their gratitude to Examiner Stockton for the telephone interview on August 12, 2009.

In the interview, Applicants' representatives discussed US Patent No. 5,270,317 ("Bernhart"), International Patent Publication No. WO99/38847 ("Anderson"), and International Patent Publication No. WO02/094816 ("Ramashankar") with the Examiner. Applicants' representatives pointed out that there would have been no motivation to replace the cyano group in the compound of formula 3 of Bernhart with a trityl-protected tetrazolyl group using the reaction conditions disclosed in Bernhart, which include the presence of a base, because one of ordinary skill in the art would have expected that the trityl group be removed in the presence of the base, as taught by, e.g., Ramashankar. The Examiner enquired about whether Applicants could present evidence showing unexpected result over Example 5 of Bernhart. The Examiner suggested that Ramashankar be submitted in an Information Disclosure Statement, which Applicants' representatives agreed.

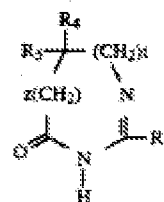
Claim Rejections – 35 USC §103 over Bernhart in view of Anderson, Cuadro, and Alvarez-Builla

Claims 11 – 30 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Bernhart in view of Anderson, Cuadro, A.M. et al, "Synthesis of N-(Aminoethyl)azoles under Phase Transfer Catalysis," *Synthetic Communications*, 21(4), 535-544, 1991 ("Cuadro"), and Alvarez-Builla J. et al, "1,5-Bis-(N-Benzyl-N,N-Diethylammonium) Diethylether, Dichloride (BBDE Cl). A Novel Bis-Ammonium Salt as Phase Transfer Catalyst," *Tetrahedron*, Vol. 46 (3), 967-978, 1990 ("Alvarez-Builla"). Applicants traverse the rejections.

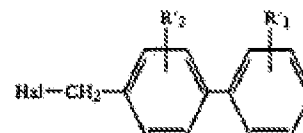
The Office contends that Bernhart teaches that it is well within the skill of one skilled in the art to convert, for example, a tetrazolyl group protected by a trityl group or a cyano group to a tetrazolyl group by known methods (col. 9, lines 15-28 of Bernhart). Applicants point out that Bernhart discloses a method a1) of preparing the compound (I) of the following formula



by reacting a heterocyclic derivative of the formula



(formula 2) with a (biphenyl-4-yl)methyl derivative of the formula

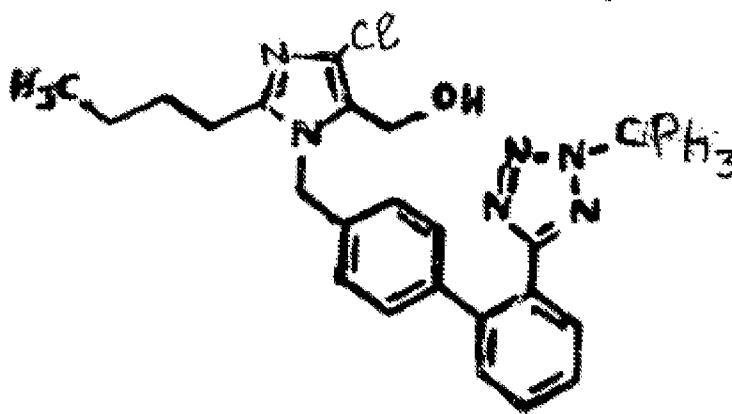


(formula 3), wherein R'_1 and R'_2 are respectively either R_1 and R_2 or a precursor group of R'_1 and R'_2 (see col. 3, line 53-col. 4, line 3). Bernhart also discloses that R_1 and R_2 are similar or different and are each independently hydrogen or a group selected from, among a list of over 20 broad substitution groups, a cyano group and a tetrazolyl group (see col. 1, lines 52-65). Bernhart further discloses that the conversion of a group R'_1 and/or R'_2 to a group R_1 and/or R_2 is effected by methods well known to those skilled in the art and that if R_1 and/or R_2 is tetrazolyl, R'_1 and/or R'_2 can either be a tetrazolyl protected for example by a trityl group, or a cyano group which cyano group is subsequently replaced with a tetrazolyl group protected for example by a trityl group (see col. 9, lines 15-24). Bernhart also discloses generally that step a1) is carried out in an inert solvent such as DMF, DMSO or THF, in a basic medium, for example in the presence of potassium hydroxide, a metal alcoholate, a metal hydride, calcium carbonate or triethylamine (see col. 9, lines 54-58).

However, Bernhart does not disclose what the “methods well known to those skilled in the art” are when R'_1 is specifically a trityl-protected tetrazolyl group. One of ordinary skill in the art would NOT have expected that the general reaction conditions disclosed in col. 9, lines

54-58 would apply for all the compounds of formula 3 despite what the substitution groups R'_1 and R'_2 are. Neither does Bernhart suggest that the same method used when R'_1 is a cyano group can be applied when R'_1 is replaced with a trityl-protected tetrazolyl group. Applicants would also point out that Bernhart does not disclose conducting the reaction between the heterocyclic derivative and the (biphenyl-4-yl)methyl derivative with phase transfer catalysis.

Bernhart discloses, in Example 5A), reacting 2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one with 4-bromomethyl-2'-cyanobiphenyl to form 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-n-butyl-4-spirocyclopentane-2-imidazolin-one. The reaction takes place in the presence of a strong base: sodium hydride. However, one of ordinary skill in the art would not have been motivated to replace the cyano group in 4-bromomethyl-2'-cyanobiphenyl with a trityl-protected tetrazolyl group in this reaction. As stated in the previously-filed Response and as pointed out during the interview, one of ordinary skill in the art would have expected that the trityl group be removed under a basic environment. For example, Ramashankar, discloses removing the trityl group from trityl losartan of the formula



, which has identical structure in the vicinity of the tetrazolyl group to trityl irbesartan, by using potassium hydroxide, a base, in an alcohol (see page 3, last paragraph-page 4, 1st paragraph and the Examples). As such, in view of Ramashankar, Bernhart does not suggest to one of ordinary skill in the art that the method disclosed in Example 5A) or in col. 9, lines 54-58 can be used when R'_1 is a trityl-protected tetrazolyl group.

Anderson discloses the N-alkylation of 2-R-1,3-diazaspiro[4.4]nonan-4-one hydrochloride by reacting with a 4'-(halomethyl)[1,1'-biphenyl]-2-carbonitrile, such as 5-(4'-

bromomethyl[1,1'-biphenyl]-2-carbonitrile, using phase-transfer catalysis (see page 6, lines 12-21 and Examples 2 and 3). Anderson merely cites Bernhart in the Background and does not teach or suggest replacing the carbonitrile (= cyano) group with a trityl-protected tetrazole group in the phase transfer catalysis reaction. Because, in view of Ramashankar, Bernhart does not teach or suggest using the same method for a cyano-substituted compound and a trityl-protected tetrazole-substituted compound, as discussed above, Anderson could not suggest it either. Further, as stated in the previously-filed Response and as pointed out during the interview, the N-alkylation using phase-transfer catalysis disclosed in Anderson, Cuadro, and Alvarez-Builla uses a base (see Anderson, Examples 2 and 3; Cuadro, N-Alkylation of Azoles General Procedure on pages 539-540; Alvarez-Builla, the N-alkylation section in Table 1 on page 970). For the same reason as stated above, one of ordinary skill in the art would not have been motivated to replace the cyano group in 5-(4'-bromomethyl[1,1'-biphenyl]-2-carbonitrile with a trityl-protected tetrazolyl group in the phase-transfer catalysis reaction disclosed in Anderson because there would have been no reasonable expectation of success since one of ordinary skill in the art would have reasonably predicted that the trityl protecting group would be removed from the tetrazolyl group in view of Ramashankar.

Additionally, Applicants further point out that although Bernhart discloses, in col. 9, lines 23-25 and Example 5B), that a cyano group needs to be subsequently replaced with a (trityl-protected) tetrazolyl group, Bernhart does not even mention that the cyano group in the 4-bromomethyl-2'-cyanobiphenyl used in step A) can be replaced with a trityl-protected tetrazolyl group, thereby eliminating the need for step B) altogether. Instead, in step B), the cyano group is converted to a trityl-protected tetrazolyl group using an azide, which is known to be extremely toxic and to tend to reduce the reaction yield. As such, the absence of any teaching/suggestion to replace the reactant in step A) to avoid an additional step and to avoid using azide is an indicator that a method applicable to $R'_1 = \text{cyano group}$ may not apply to $R'_1 = \text{trityl-protected tetrazolyl group}$. Furthermore, Anderson, which is a later publication to Bernhart and expressly cites Bernhart, is directed to the N-alkylation of 4'-(halomethyl)[1,1'-biphenyl]-2-carbonitrile using phase-transfer catalysis conditions. Anderson refers to Bernhart for the conversion from the cyano group is converted to a trityl protected tetrazolyl group. Anderson does not mention that the carbonitrile group can be replaced by a trityl protected tetrazolyl group in the phase transfer

catalysis reaction, despite the fact that doing so can eliminate the later conversion step. The absence of such teaching/suggestion to replace the reactant in the phase transfer catalysis reaction to avoid an additional step and to avoid using azide in Anderson is a further indicator that one of ordinary skill in the art would not have been motivated to use a trityl-protected tetrazole-substituted compound as the reactant in the phase transfer catalysis reaction of Anderson.

The deficiency of Bernhart and Anderson is not cured by Cuadro or Alvarez-Builla, because none of Cuadro and Alvarez-Builla teaches or suggests that a trityl-protected tetrazole-substituted compound, such as 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole as recited in claim 1, can undergo N-alkylation using the phase-transfer catalysis conditions disclosed in Anderson, Cuadro, or Alvarez-Builla.

For at least the reasons stated above, a *prima facie* case of obviousness has not been established. Withdrawal of the rejections is respectfully requested.

CONCLUSION

Applicants submit that the claims are allowable. An early and favorable action to that effect is respectfully requested.

The Examiner is invited to contact the undersigned to discuss any issues regarding this response.

In the event that the filing of this paper is deemed not timely, applicants petition for an appropriate extension of time. The Office is authorized to charge any underpayment or credit any overpayment to Kenyon & Kenyon LLP's Deposit Account No. 11-0600.

Respectfully submitted,
KENYON & KENYON LLP



Date: August 12, 2009

By: _____

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